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EXAMINER

ART UNIT	PAPER NUMBER
1802	9

18M1/1126

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DATE MAILED: 11/26/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 10/21/96 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-21 are pending in the application.
   Of the above, claims 2-5, 14-15 & 18-21 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1, 6-13 & 16-17 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 1-16 are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I and Species III in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the instant application has unity of invention because the coated paramagnetic particles are not obvious over the prior art. Applicant argues that the method of using the coated paramagnetic particles of the instant invention achieves close to 100% specific binding and thus is able to select target cells with a very high degree of purity compared to methods of the prior art. This argument is not persuasive because the method of the instant invention is obvious over Widder et al in view of Connelly et al and Forrest et al for reasons of record in paper number 7. Further, Applicant's argument directed toward the binding specificity of the paramagnetic particles is not on point since this is not a limitation recited in the instant claims.

Applicant argues that a factor for obtaining the specificity is that the cells are kept at 4°C during the procedure until microscopy. This argument is not persuasive because the instant claims recite that the cells are incubated at a temperature between 0°C and 20°C with a preferred temperature being 4°C. The incubating range is obvious over the prior art and is specifically taught by Connelly.

Applicant argues that the paramagnetic or superparamagnetic particles of the instant invention have very high magnetic attraction capacity and that this is not taught by the prior art. This argument is not persuasive because magnetic capacities are not recited in the instant claims.

Applicant argues that Connelly et al teach the use of fixatives which is not warranted or required for the purposes of the instant application. This argument is not persuasive because the method Applicant's claims required the use of fixatives such as formalin or alcohol, which is seen to be obvious over Connelly et al.

Applicant argues that Forrest et al does not teach an assay to detect cells, but only soluble antigens. This argument is not persuasive because the Forrest et al is relied upon for the teaching of avidin/biotin. Applicant is reminded that references cannot be argued separately but rather, arguments should be directed to the combined teachings of the cited references.

Applicant argues that the instant application has unity of invention as was found by the International Preliminary Examination Authority. This argument is not persuasive because this Examiner is not bound by the findings or opinion of other Examiners.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 2-5 and 14-15 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 7.

3. Newly submitted claims 18-21 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the method of characterizing specific genes of the separated cells at the DNA, mRNA, protein level, polymerase chain reaction or reverse transcriptase PCR is not related to the method of separating a target cell population from a population of mixed cells because these later methods required completely different method steps and reagents. Likewise, the method of establishing in vitro cells cultures, inoculating immunodeficient animals to establish a human tumor xenograft is not related to the method of separating a target cell population from a population of mixed cells.

Since applicant has received an action for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 18-21 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. This application contains claims 2-5, 14-15 and 18-21 drawn to an invention non-elected with traverse in Paper No. 7.

Specification

5. The disclosure is objected to because of the following informalities:

Page 5, 2nd ¶, "Flowcytometric" should be --Flow cytometric--.

Page 7, middle of 1st ¶, "gastrointestial" should be --gastrointestinal--.

Page 10, 3rd ¶, "bllod" should be --blood--.

Page 11, 1st ¶, "warrented" should be --warranted--. 2nd ¶, "warrantied" should be --warranted--. 3rd ¶, 7th line, "our" should be deleted. 5th ¶, "caoted" should be --coated--.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. Claims 1, 6-13 and 16-17 are rejected under 35 U.S.C. 112, second paragraph, as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is confusing with respect to the use of "1.1, 1.2.1, 1.2.2, 1.3, 1.4.1, 1.4.2, 1.4.3, 1.5.1, and 1.5.2". Applicant should use --a, b, (i), c, d, (i), (ii), e and (i)-- respectively to obviate the rejection.

Claim 16 is confusing with respect to the use of "1, 2, 3, and 4". Applicant should use --a, b, c and d-- respectively to obviate the rejection.

Claim 1 is vague and indefinite with respect to the use of "malign haematopietic cells" because of the use of nonidiomatic English. "Malign" should be --malignant-- and "haematopietic" should be --hematopoietic--.

Claim 1 is vague and indefinite with respect to the use of "capable of" because it is unclear if the coated antibodies do or do not bind to the Fc portion of the other antibodies. The use of "the said antibodies" is confusing because it is unclear which antibodies this is referring to. The use of "the target-cell-associating antibodies" lacks antecedent support. The use of "(murine or human)" is parenthetical and does not provide positive limitation to the claim. The use of "free target-cells-associating antibodies" lacks antecedent support. The use of "suitable concentrations" is vague because it is unclear how much material defines a "suitable concentration". The use of "the ..untreated" in part 1.4.2 lacks antecedent support. The use of "other antibodies" in part 1.4.2 is confusing because it is unclear what other antibodies this is referring to. The use of "the antibodies" in the last line bridging page 2 and 3 of preliminary amendment A is confusing because it is unclear which antibodies this is referring to. The use of "the binding" lacks antecedent support. The use of "the antibody fragments" is confusing because

it is unclear which antibody fragments this is referring to. The use of "the incubating" is confusing because it lacks antecedent support and is nonidiomatic English.

Claim 6 is vague and indefinite because it depends on a non-elected claim. For the purpose of examination, Examiner assumes that claim 6 depends on claim 1.

Claim 7 is vague and indefinite with respect to the recitation of 'the said target-cell associating antibodies" because it lacks antecedent support.

Claim 8 is vague and indefinite with respect to the use of improper Markush language. The members of the Markush group must be equivalent and the last two members of the Markush group must be connected by and --and--.

Claims 9 -12 are vague and indefinite with respect to the referral to Table 1 of the specification because this does not provide positive limitations to the claims.

Claim 12 is vague and indefinite with respect to the recitation of "the used antibodies" because it lacks antecedent support.

Claim 13 is vague and indefinite with respect to the recitation of "the said antibody" because it lacks antecedent support.

Claim 16 is vague and indefinite because it depends on a non-elected claim. Examiner assumes that claim 16 is dependent on claim 1 for the purpose of examination on the merit. Claim 16 is vague and indefinite with respect to the recitation of "the antigen receptors" and "the wanted targed-cells" because they lack antecedent support. The recitation of "can be bound" is vague and indefinite because it is unclear if the antibody is or is not bound to the paramagnetic particles. The recitation of "can be bound to included paramagnetic particles" is non-idiomatic English. The recitation of "and/or" is confusing. The recitation of "capable of binding" is vague and indefinite because it does not provide positive limitation to the claim.

Claim 17 is vague and indefinite because it does not further limit the subject matter of the independent claim from which it depends.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 7 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Widder et al (EP 016,552) in view of Connelly et al (US Patent No. 5,422,277), Forrest et al (US Patent No. 4,659,678), and Pilling et al (Journal of Immunological Methods, 1989).

Widder et al teach magnetically-responsive microspheres having Protein A associated with the surfaces and further reacted with select antibodies before the microspheres are used for cell separation (column 2, lines 48-55). Widder et al teach magnetic microspheres containing Protein A coupled with FITC-conjugated rabbit IgG by incubation at 37°C for 20 minutes and examined. The intensity and uniform distribution of fluorescence indicated that Protein A was oriented on the microspheres surface in a manner that allowed IgG molecules to interact with the Fc binding sites on the Protein A (column 6, example 1). Widder et al teach using the coated particles to separate red blood cells (RBC) from suspensions containing a mixture of different RBCs. The RBCs are labeled with ^{51}Cr and incubated with the IgG-coated microspheres for 30 minutes at 37°C with mild agitation. Cells were separated and counted using a gamma counter (column 7, example 2).

Widder et al differ from the instant invention in failing to teach the use of enzyme labels and an avidin/biotin binding system. Widder et al also do not teach using fixatives to pretreat the sample.

Connelly et al teach various fixatives used to fix cells without destroying cellular properties. Connelly et al teach that the treatment reagent is capable of permeating the cell and fixing it while preserving both the immunoreactivity and light scatter of such cell (column 3, lines 34-46). Connelly et al teach fixing cells with phosphate buffered solution followed by DMSO and DNBS, Tween™ and formaldehyde (column 9, lines 10-14). Connelly et al teach incubating the cells with the fixative for about 20 minutes to 2 hours at temperatures ranging from 0°C to about 37°C. Connelly et al teach that the fixative composition is used in the fixing of bone marrow and blood cells, and fixed cells can then be examined by any suitable technique known to the art such as through the use of a microscope, immunofluorescence or flow cytometry (column 9, lines 45-48).

Forrest et al teach a sandwich assay using solid supports such as particles or beads having labeled or unlabeled antibodies attached thereto. The label employed maybe selected from those known in the art such as fluorimetric or enzyme labeling. Forrest et al also teach using Protein A attached to the solid support and further attached to an antibody (columns 3-4). Forrest et al teach using reagents that constitute a specific binding protein such as avidin and biotin and adding the reagents in any order so as to optimize the reaction conditions (column 5).

Pilling et al teach positive immunoselection procedures using specific antibodies to isolate cells which express particular suface determinants. Pilling et al teach coating magnetic particles with monoclonal antibodies and incubating the coated particles with a mixed population of cells to effect separation of cells of interest from the rest of the cells in the sample. Pilling et al teach incubating the coated beads with CD4+ T cells and monoclonal antibody for 30 minutes at 4°C and separate the beads by magnetic attraction (page 237, Simultaneous Dynabeads rosetting and fluorescence labelling).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to pretreat the sample of Widder et al using the fixatives taught by Connelly et al because

Connelly et al teach that fixed cells are useful in monitoring blood cells for viral burdens by enhancing the measurement of viral components in a sample and Widder et al teach that their method of magnetic separation is used to identify a specific cell type, bacterial or viruses, thus the fixatives of Connelly et al provide an improved method of identifying a specific component of a sample. The fixatives of Connelly et al are also useful in providing means to fix cells without destroying cellular properties thus allowing one to analyze the cells in details. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use binding system such as avidin/biotin, as taught by Forrest et al, because Forrest et al teach that avidin/biotin provides a very rapid and high affinity binding which offers the advantage that a reaction can be made very rapid and complete. The use of "double-antibody layer", i.e. Protein A-Ig, is also well known in the art and a skill artisan would have had a reasonable expectation of success in using such double layer because Widder et al teach that such microspheres are effective for antigen binding and use in magnetic sorting procedures is thereby maximized which greatly increases the efficiency with which the select antibodies may be used. It also eliminates the need for chemical coupling of the antibodies. Incubation temperature and time are easily modified by a skilled artisan to optimize reaction conditions as taught by Pilling et al.

9. Claims 6, 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Widder et al in view of Connelly et al, Forrest et al and Pilling et al as applied to claims 1, 7 and 17 above, and further in view of Kemmer et al (Journal of Immunological Methods, 1992) and Holmes et al (WO 91/09938).

See discussion of Widder et al, Connelly et al and Forrest et al above. Widder et al differ from the instant invention in failing to teach the type of cells or cell samples that may be separated from a medium.

Kemmer et al teach isolation of tumor cells from a mixed cell suspension of human tumor tissue which contains tumor cells, leukocytes and erythrocytes, using magnetic beads coated with monoclonal antibodies.

Holmes et al teach a method of separating haemopoietic progenitor cells from a mixed population of haemopoietic cells which contain malignant cells using magnetic microbeads coated

with sheep-anti mouse antibody which binds to the Fc portions of IgG mouse antibodies or Protein A which reacts universally which the Fc portion of virtually all IgG antibodies (page 6, lines 8-24). The mixed population of Homes et al is commonly derived from bone marrow mononuclear cells and fetal and umbilical cord blood or adult human blood.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of cell separation taught by Widder et al, as modified by Connelly et al and Forrest et al, to separate cells from a variety of cell samples as taught by Kemmer et al and Holmes et al, because Kemmer et al and Holmes et al teach that it is advantageous to remove tumor cells from a mixed cell suspension using magnetic microbeads coated with either monoclonal antibodies or Protein A for the purpose of further studying the tumor cells or to purge a sample of tumor cells. The use of various monoclonal antibodies specific for antigens present on the cell surface is well known in the art and a skilled artisan would have had a reasonable expectation of success in choosing an antibody that is specific for an antigen present on the surface of the cell population of interest.

10. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Widder et al in view of Connelly et al, Forrest et al and Pilling et al as applied to claims 1, 7 and 17 above, and further in view of Afseth et al (WO 91/15766).

See discussion of Widder et al, Connelly et al, Forrest et al and Pilling et al above. Widder et al differ from the instant invention in failing to teach assembling the reagents into a kit.

Afseth et al teach a method of cell isolation using magnetic particles coated with polyclonal or monoclonal antibodies. Afseth et al teach that the method may be use for isolation of malignant cells or cell populations specific for different diseases and to characterize these cells further without interference from other contaminating cells. Afseth et al also teach that the method may be use to isolate protective cell populations, expanded or potentiated and returned to a patient under treatment (pages 5-6). Afseth et al also teach assembling the reagents necessary for the method into a kit (page 8).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to assemble the reagents taught by Widder et al, Connelly et al and Forrest et al into a kit as

taught by Afseth et al because Afseth et al teach that the use of kits is convenient and economical. A skilled artisan would have had a reasonable expectation of success in assembling all of the reagents necessary for the assay into a kit because the immunoassay kits are well known in the art.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao-Thuy Nguyen whose telephone number is (703) 308-4243. The examiner can usually be reached Monday through Friday, from 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

BTN
November 22, 1996

Christopher L. Chin
CHRISTOPHER L CHIN
PATENT EXAMINER
GROUP 1800